Letter to the Editor: Immortal Time Bias or Sorafenib Effect in Elderly Patients with HCC?

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Editor-in-Chief, Hepatology

RE: Parikh et al, Hepatology 2017; 65 (1): 122-133

To the editor,

In the January 2017 issue of *Hepatology*, Dr. Parikh and colleagues reported on the important topic of the clinical and cost effectiveness of sorafenib for advanced hepatocellular carcinoma (HCC). Using the SEER-Medicare database, they found patients treated with sorafenib had significantly longer survival than untreated patients; hazard ratio (HR) 0.66 (95%CI 0.57-0.77). Similar benefit was seen in patients with decompensated cirrhosis, and after propensity score matching. With an incremental cost-effectiveness ratio of $84,250, the authors concluded sorafenib was both effective and cost-effective in this population.

These findings were striking to us, as in September 2016 we reported on the effectiveness of sorafenib in advanced HCC using the same data source and similar methods.(1) We found sorafenib treated patients did not survive longer than untreated patients; HR 0.95 (95%CI 0.78-1.16). We believe that immortal time bias is the primary reason for the discrepant findings.

Immortal time bias occurs in observational comparative effectiveness studies when follow-up begins before treatment status has been assigned. This temporal misalignment leads to guaranteed or “immortal” person-time in patients who initiate treatment (versus those who do not) as individuals must survive to be classified as a treatment initiator.(2, 3) In Dr. Parikh’s study, patients were included in the sorafenib group if they initiated sorafenib within 6 months of diagnosis, despite a median survival in the cohort of 90 days. Thus, immortal person-time accrued for the sorafenib group between diagnosis and sorafenib initiation, leading to artificially protective treatment effects. At 90 days there was already a 23.4% absolute improvement in survival for sorafenib, at least partially attributable to accrual of immortal time.

Parikh and colleagues addressed immortal time bias by conducting a sensitivity analysis in which sorafenib was included as a time-dependent exposure; this attenuated the treatment effect; HR 0.87 (95%CI 0.74-1.01). However, to adequately evaluate the effect of time-varying sorafenib initiation on mortality, the analysis must also address time-varying cofounding. Changes in the health status of HCC patients occur quickly, and such changes unequivocally affect the likelihood of sorafenib initiation and survival. Without consideration of such time-varying confounders using appropriate statistical methods,(4) the attenuated survival benefit from sorafenib is likely still biased.

Immortal time bias is a major concern when analyzing the effectiveness of sorafenib for advanced HCC in observational data because of the exceptionally high rates of early death in

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this population. Therefore, we recommend caution when interpreting the conclusion of Parikh and colleagues that sorafenib improves survival and is cost-effective in Medicare beneficiaries.

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Conflict of Interest
Dr. Sanoff has received research funding from Bayer, Novartis, Merck, Precision Biologics, and Immunomedics. Dr. Lund's spouse is an employee of GlaxoSmithKline. Dr. O'Neil has received research funding from Bayer and has served as a consultant for Bayer. Drs. Chang and Dusetzina report no conflicts.

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